REMARKS

I. Rejection of Claims as Obvious over Richardson, et al

Claims 11 to 13 were rejected as obvious under 35 U.S.C. 103 (a) over Richardson, et al.

Richardson, et al, clearly state: "Supplemental melatonin for glaucoma patients to reduce hyperinsulinemia is therefore physiologically sound, and would be appropriate." See column 12, lines 30 to 34. However the compositions for treating patients, including tablets and the like, disclosed by Richardson, et al, only recommend melatonin as an optional agent for treating hyperinsulinemia. Claims 1 to 12 of Richardson, et al, do not even mention melatonin! They also list and in some cases prefer Chrominum, Vanadium, α-lipoic acid and nicotinamide in columns 11 and 12.

Preferred dosages of melatonin for administration in their compositions are given in columns 17 and 18. Richardson, et al, teaches administration of large dosages of melatonin in column 17 (80 mg) and melatonin dosage ranges in Table I and Table II, last lines, namely 0.05 to 10 mg.

These latter dosages clearly fall within the range taught in claim 11, of 0.01 to 200 mg.

However Richardson, et al, U.S. Patent 6,207,190 B1 is **not** a valid prior art reference against the claims of the above-identified U.S. Patent Application, which is entitled to the benefit of the priority date of German Application 198 23 829.0, namely May 28, 1998, the filing date of this application in Germany. This

latter German application is the priority document for PCT/DE 99/01541. The above-identified U.S. Patent Application, Ser. No. 09/701,334, is the U.S. National Stage of PCT/DE 99/01541.

Richardson, et al, is entitled only to the benefit of the application date of the provisional application on which it is based dated August 13, 1998 (see the cross-reference in column 1). Thus Richardson, et al, is not a valid reference against the above-identified U.S. Patent Application, which has an effective date of May 28, 1998, the filing date of German application 198 23 829.0.

An Official copy of the German priority document 198 23 829.0 is being filed with this amendment. Also the specification and claims filed in the PCT application are the same as in the German Application filed in Germany. A certified English translation of the PCT application was filed with the application papers in the above-identified U.S. Patent Application. A translator's certification accompanies this amendment, which states that the U.S. application is a certified English translation of the German application 198 23 829.0.

Thus Richardson, et al, is not a valid prior art reference that can be used to reject the claims of the above-identified U.S. Patent Application.

For the foregoing reasons withdrawal of the rejection of claims 11 to 13 under 35 U.S.C. 103 (a) as obvious over Richardson, et al, is respectfully requested.

II. Rejection under 35 U.S.C. 112, First Paragraph

Claims 11 to 13 were rejected under 35 U.S.C. 112, first paragraph, for lacking enablement.

Method of treatment claims 11 to 13 have not been changed.

Claim 11 claims an *in vivo* method of administering an effective dosage of melatonin to a person to treat hyperinsulinemia.

First, the present application and claim 11 do give some guidance regarding the dosage for *in vivo* administration of melatonin to treat hyperinsulinemia in humans as well as some guidance regarding *in vivo* methods of administration. The dosage range given in claim 11 is 0.01 to 200 mg.

Second, the standard for the amount of guidance required to support claims for a method of *in vivo* administration should not be any greater for applicants than the guidance required to support the claims granted to Richardson, et al. Claims 19, 21, 22 and 24 were granted to Richardson, et al, for unit dosage forms containing melatonin as hyperinsulinemia modulation agent with little more data regarding utility of the composition of method of administration than in the case of the applicants' disclosure.

Applicants teach specific methods of administration, such as those listed in the dependent claims and a dosage range of 0.01 to 200 mg. Richardson, et al, teach administering large amounts of 80 mg of melatonin and a range of 0.05 to 10 mg, as mentioned above. Thus the range taught by Richardson, et al, is more or less equivalent to 0.05 to 80 mg, which is not significantly different from

that of the applicants, namely 0.01 to 200 mg. However Richardson, et al. do not provide any clinical test data in their examples that show that melatonin administered in this sort of in vivo method is effective to reduce the levels of insulin. Richardson, et al, do not provide experimental tests of any kind to support their claim that melatonin in the administered amount is effective in treating hyperinsulinemia or reducing insulin levels, either *in vivo* or *in vitro*.

Third, U.S. Patents including claims for *in vivo* methods of treatment have been granted on the basis of *in vitro* experimental data. U.S. Patent 6,172,056 B1 claims methods of prophylaxis and therapy of radical-mediated cell damage by administering to a human being at least one steroid selected from a group of steroid derivatives that had not been previously tested for this purpose. These steroid derivatives were tested for effectiveness in lipid peroxidation inhibition and LDL oxidation inhibition by entirely *in vitro* methods. There was no requirement during prosecution to make *in vivo* tests. A copy of U.S. Patent 6,172,056 B1 is being filed together with an information disclosure statement.

Furthermore additional *in vitro* experimental results showing that melatonin is effective in inhibition of insulin release that is stimulated by glucose or KCl as provided in the article, *J. Pineal. Res.* 1997, 23, pp. 156 to 163. These additional results support claims 14 to 17 as well as claims 11 to 13. This article was previously used together with Bailey, et al to reject the claimed invention as obvious under 35 U.S.C. 103 (a). However the article was the result of the work of applicants in the above-identified U.S. Patent Application and it was eliminated as a valid prior art reference by filing a Declaration under 37 C.F.R. 1.131, i.e. by

swearing back of the reference.

Furthermore detailed methods of preparing tablets, ampoules, adhesive tape, subcutaneous implants and the like are thus better left out of the patent and left to those of ordinary skill in the art because those methods are well known in the pharmaceutical arts.

It is well established that what is well known in the art is better left out from a patent specification. For example the Federal Circuit Court of Appeals has said:

> "A patent need not teach, and preferably omits, what is well known in the art". ***Hybritech Inc. v. Monoclonal Antibodies, Inc.***, 231 U.S.P.Q. 81(Fed. Cir. 1986).

The test of enablement is whether or not undue experimentation is required to practice the invention. See M.P.E.P. 2164.01. As a short guide to what is undue experimentation the Federal Circuit found that experimentation was **not** undue when $50,000 and 6 to 12 months of experimentation was required in *United States v. Telectronics, Inc.*, 8 U.S.P.Q. 2nd 1217 (Fed. Cir. 1988).

All that is required to better establish the exact preferred dosages for melatonin within the claimed range of claim 11, 0.01 to 200 mg, is some experimentation with model systems (such as mice or guinea pigs) with various dosages within this ranges, which is routine for pharmaceutical and academic laboratories.

Thus it seems that the situation here would satisfy the test of enablement in the M.P.E.P. Undue experimentation is <u>not</u> required to arrive at an effective *in*

vivo method of treating hyperinsulinemia from the disclosures in applicants specification.

It is well to remember that compliance with the enablement requirement under 35 U.S.C. 112, 1st paragraph, (in contrast to the statement on page 4 of the Office Action) does **not** turn on whether or not a working example has been provided. See M.P.E.P. 2164.02 and the case law cited therein.

As long as the method of administration results in the transport of the melatonin to the G protein-coupled membrane-bound receptors intact, excessive insulin production should be suppressed or reduced to a significant extent as shown by the *in vitro* experiments of figs. 1 and 2 of the applicants' specification and the J. Pineal Res. article. Clearly some of the methods of administration mentioned on page 3 are preferable to others for this purpose, such as the subcutaneous implantation route, but undue experimentation is not necessary for one skilled in the art to practice the method of claim 11.

In addition the disclosures of Richardson, et al, support a conclusion that oral administration of a tablet including the effective ingredients comprising melatonin can be used in a method of treating hyperinsulinemia in a human being (column 22).

For the foregoing reasons withdrawal of the rejection of amended claims 11 to 13 under 35 U.S.C. 112, first paragraph, for lack of enablement is respectfully requested.

III. Withdrawal of Claims 14 to 17

Newly submitted method claims 14 to 17 were withdrawn from consideration because they are directed to a different method than claims 11 to 13 in accordance with 37 C.F.R. 1.142 (b). Claims 11 to 13 are indeed drawn to an *in vivo* method of treating hyperinsulinaemia. Claims 14 to 17 are drawn to a method of reducing insulin release from pancreatic islets *in vitro*.

However reconsideration of the withdrawal of claims 14 to 17 is respectfully requested. Reinstatement of claims 14 to 17 and prosecution of these claims 11 to 13 together with claims 11 to 13 is requested because this application is the U.S. National Stage of PCT/DE 99/01541 and thus "unity of invention" practice applies here and because canceled claim 1 is, according to the Office Action dated July 26, 2002 (paper # 6), equivalent to new claim 14 (both claims have already been interpreted by the U.S. Patent Office as claims for an *in vitro* method for suppressing insulin release from pancreatic islets).

The Office Action dated July 26, 2002 reported an Examination of the original claim 1 of the above-identified U.S. Patent Application. This original claim 1 was the English translation of a foreign patent document (priority document) and was in the form of a "use" claim, which is non-statutory in U.S. Patent Practice. Thus there is some prima facie doubt regarding the interpretation of this sort of claims during an examination of it on the merits. However the Office Action dated July 26, 2002 (paragraph 11, page 6) removed that doubt and interpreted claim 1 as a claim for a method of using melatonin to depress

glucose-stimulated insulin section from mouse islets. New claim 14 claims a method of administering melatonin to pancreatic islets to reduce insulin secretion.

Thus claim 14 is not a new claim at all but claims the subject matter that was filed in the original canceled claim 1, according to the interpretation in the Office Action dated July 26, 2002. M.P.E.P. 1.142 (b) states that if claims for an invention that was not originally elected are presented at a later stage in the prosecution, they should be withdrawn. The reason given on page 2 of the latest Office Action is that claim 14 is drawn to a method that was not originally considered on the merits and would thus require a new search of the prior art. However that is not the situation since the original canceled "use" claim 1 was interpreted as if it contained the same subject matter as claim 14 and was examined on the merits.

For the foregoing reasons reinstatement and examination of claims 14 to 17 is respectfully requested.

Furthermore the different methods according to claims 14 to 17 and claims 11 to 13 should be prosecuted in the same application because "unity of invention" practice applies here since this is a U.S. National Stage application of the PCT International Application, PCT/DE 99/01541.

However in accordance with 37 C.F.R. 1.143 applicants *provisionally* elect to continue prosecution with claims 11 to 13, but the restriction requirement is hereby respectfully traversed for the above reasons.

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

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